PB91-161653

Ambient Water Quality Criteria Document Addendum for Phthalate Esters

(U.S.) Environmental Protection Agency, Cincinnati, OH

Sep 89

U.S. Department of Commerce
National Technical Information Service
NTIS

REPORT DOCUMENTATION PAGE

Form Approved
OMB No 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1 PB91-161653	2. REPORT DATE September, 1988	3. REPORT TYPE AND DATES COVERED

4. TITLE AND SUBTITLE
Ambient Water Quality Criteria Document Addendum for Phthalate Esters.

5. FUNDING NUMBERS

6. AUTHOR(S)
Criteria Branch/Office of Water Regulations & Standards

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
U.S. EPA/Office of Water Regulations & Standards
Criteria Branch (WH-585)
401 M Street SW
Washington, D.C. 20460

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Addendum to PB 81-117780

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five jears. These addenda represent an updated literature search current as of 1988, plus additional information form Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Phthalate Esters.

14. SUBJECT TERMS	15. NUMBER OF PAGES 41
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
unclassified	unclassified	unclassified	unlimited release

United States
Environmental Protection
Agency

FINAL DRAFT
ECAO-CIN-665
September, 1989

EPA

Research and Development

PB91-161653

AMBIENT WATER QUALITY CRITERIA DOCUMENT
ADDENDUM FOR PHTHALATE ESTERS

Prepared for

OFFICE OF WATER REGULATIONS
AND STANDARDS

Prepared by

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DRAFT: DO NOT CITE OR QUOTE

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CRAVE	Carcinogen Risk Assessment Verification Endeavor
DWEL	Drinking water equivalent level
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RFD	Reference dose
RQ	Reportable quantity
TLV	Threshold limit value
TWA	Time-weighted average

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RfD = \frac{\text{NOAEL or LOAEL}}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQC on phthalate esters, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

Toxicologic/Carcinogenic Effects

Phthalate has three isomers (ortho, meta and para positions); the term phthalic acid esters generally refers to esters formed from the ortho phthalic acid isomer. U.S. EPA (1980) reviewed eight ortho phthalic acid esters: butyl benzyl phthalate, butylphthalyl butylglycolate, dibutyl phthalate, diethyl phthalate, di(2-ethylhexyl)phthalate, dimethyl phthalate, di-N-octyl phthalate and ethylphthalyl ethylglycolate. None of the phthalic acid esters were found to be carcinogenic in animals or humans in the literature available to U.S. EPA (1980). However, the U.S. EPA (1982) reevaluated the carcinogenicity of di(2-ethylhexyl)phthalate and stated this compound is "suspected of being a human carcinogen." New data described below suggest that butyl benzyl phthalate is a possible human carcinogen (Group C), and that di(2-ethylhexyl)phthalate is a probable human carcinogen (Group B2). More recent toxicologic studies on butylbenzyl phthalate, dibutyl phthalate, diethyl phthalate, di(2-ethylhexyl)phthalate and di-N-octyl phthalate have also been reported in the literature. Pertinent new studies concerning the toxicologic or carcinogenic effects of dimethyl phthalate, butylphthalyl butylglycolate and ethylphthalyl ethylglycolate were not found in the available literature.

Butyl Benzyl Phthalate

Ambient water quality criteria were not derived for butyl benzyl phthalate by the U.S. EPA (1980) because of the lack of available data. New data suggest that butyl benzyl phthalate is carcinogenic to rats, and U.S. EPA (1987a) has verified it as a Group C compound - possible human carcinogen.

NTP (1982a) conducted a subchronic range-finding study and a carcinogenicity study in F344/N rats and B6C3F1 mice. Based on findings from the subchronic study, diets containing 0, 6000 or 12,000 ppm of butyl benzyl phthalate were selected for feeding to groups of male and female rats and mice (50/sex/group) for 103 weeks. Because of poor survival among male rats, those that were still alive at 28 weeks were sacrificed. Endpoints monitored were body weight, food consumption, mortality, clinical toxicity effects, and gross and microscopic pathology. Compound-related effects, compared with controls, included increased mortality from internal hemorrhaging (at the 14th week of exposure in male rats) and reduced body weights in female rats and in both sexes of mice. Food consumption was decreased in female rats, but data concerning this endpoint were not reported for mice and male rats. Among high-dose female rats, mononuclear cell leukemia was increased significantly (and frequently accompanied by splenomegaly and hepatomegaly), as were the incidences of neoplastic and nonneoplastic lesions. No compound-related increases in incidences of neoplastic or nonneoplastic lesions were observed in mice of either sex. Significant dose-related decreases in alveolar/bronchiolar adenomas or carcinomas, lymphomas and leukemia were noted among male mice. Female mice had significant dose-related decreases in mammary gland adenomas. NTP (1982a) concluded that n-butyl benzyl phthalate was "probably carcinogenic for female F344/N rats." Kluwe et al. (1982a) questioned this conclusion, suggesting that the normally high background incidence of myelomonocytic leukemia among F344/N rats rendered the data at best, equivocal. The decreases in mouse tumor incidence added to the uncertainty that n-butyl benzyl phthalate might be carcinogenic in humans. The U.S. EPA (1987a) determined that, although

the equivocal data raised questions, the positive finding of increased incidence of mononuclear cell leukemia in female rats could not be discounted. NTP (1989) states that a two-year feeding study is in progress for this compound.

Agarwal et al. (1985) administered butyl benzyl phthalate to male Fischer 344 rats at dietary levels of 0, 0.625, 1.25, 2.5 and 5.0% for 14 days (corresponding to daily butyl benzyl phthalate intakes of 0, 375, 750, 1250 and 1667 mg/kg/day, respectively). Significant increases were noted in liver and kidney weights at the 0.625% and 1.25% levels. At $\geq$2.5%, decreased body weight, slightly decreased food consumption, histologic atrophy of testes and accessory sex organs, and decreased bone marrow cellularity were reported.

NTP (1985) described a 26-week dietary study in F344 rats. A diet containing 0, 0.03, 0.09, 0.28, 0.83 or 2.5% butyl benzyl phthalate (0, 17, 51, 159, 470 or 1417 mg/kg/day) was fed to groups of 15 males, starting at age 6 weeks. In this study powdered rodent meal was provided in such a way that measured food consumption at the highest dose level could include significant waste and spillage rather than true food intake. For this reason a standard food consumption rate of 5% rat body weight was used in the 2.5% dose conversion. A LOAEL of 2.5% for testicular effects was identified. All rats given this dose level had small testes upon gross necropsy at 26 weeks, some had soft testes (5/11) and small prostate and seminal vesicles (1/11), six animals had infarct-like atrophy of the kidney cortex and some had testicular lesions (number not reported). Liver-to-body weight ratios increased and body weight gain was depressed significantly throughout the study at the two highest dose levels. A LOAEL for increased liver weights was identified at 0.83% butyl benzyl phthalate. NTP (1985)

also described a mating trial study in F344 rats, in which similar histopathologic changes were noted at the 2.5% butyl benzyl phthalate level. Ten of 30 females successfully mated with males in the 2.5% treatment group, but no impregnations resulted. No treatment-related effects were noted at ≤0.83%. An examination of the results reported by NTP (1985), as reported in U.S. EPA (1987b), indicated that hematologic alterations could be observed at the 2.5% dosage level.

In an addendum to the NTP (1985) final report, evaluation of the data revealed a significantly reduced total marrow cell count in the 2.5% dose group (NTP, 1986). The change in total cell count was comprised primarily of significant decreases in neutrophil, metamyelocytes, bands, segmeters, lymphocytes and leasophilic rubricytes. The total marrow cell counts, metamyelocyte and leasophilic rubicyte counts were also significantly decreased in the lowest dose group, 0.03%. No statistically significant differences were noted in the middle dose groups (0.09, 0.28 or 0.83%) when compared with controls. The addendum states that decreased total marrow cell count in the 0.03 and 2.5% dose group represents a change of uncertain meaning in light of the systemic effects noted in the middle dose groups.

Butylphthalyl Butylglycolate

Pertinent new studies concerning the toxicologic or carcinogenic effects of butylphthalyl butylglycolate were not located in the available literature.

This chemical has not been evaluated by U.S. EPA for evidence of potential human carcinogenicity (U.S. EPA, 1988a).

Dibutyl Phthalate

The ambient water quality criteria for dibutyl phthalate (U.S. EPA, 1980) and the current verified RfD for oral exposure are based on the 1-year toxicity study in male rats reported by Smith (1953). Dibutyl phthalate is

verified as Group D - not classifiable as to human carcinogenicity because of the lack of adequate data from human or animal exposures (U.S. EPA, 1987c).

Lamb et al. (1987) conducted a reproductive and fertility assessment on CD-1 mice, following a test protocol called "fertility assessment by continuous breeding" (see Diethyl Phthalate section). In this study, no adverse effects on reproduction, fertility or organ weights were observed in two generations of mice fed diets containing 0.03 or 0.3% dibutyl phthalate. Reductions in numbers of litters/pair, live pups/litter and the proportion of pups born alive occurred, however, at the 1.0% level of dibutyl phthalate. The results of crossover mating showed that only the female mice were affected. The LOAEL of 1% from this study is higher than that in the study of Smith (1953), on which the verified RfD is based.

Diethyl Phthalate

The U.S. EPA (1980) derived ambient water quality criteria for diethyl phthalate based on the toxicity data from a 2-year study by Food Research Laboratories, Inc. (1955), in which rats fed 5% diets of diethyl phthalate suffered small but significant decreases in growth rates.

A subchronic oral feeding study by Brown et al. (1978), which was not discussed in the 1980 AWQCD, serves as the basis for the derivation of the verified oral RfD for diethyl phthalate. Groups of 15/sex CD (Sprague-Dawley derived) rats were exposed to dietary levels of 0, 0.2, 1.0 or 5.0% diethyl phthalate for 16 weeks. Estimated mean intakes derived by the authors were 0, 150, 770 and 3160 mg/kg/day for males, and 0, 150, 750 and 3710 mg/kg/day for females. Endpoints monitored were body weight, food consumption, water intake, urinalysis, hematology, serum biochemistry, and gross and microscopic pathology. Weight gain and food consumption were

reduced significantly in both sexes exposed to 5% diethyl phthalate and in females given 1% diethyl phthalate. Absolute weights of brain, spleen, heart and kidneys were reduced in both sexes fed 5% diethyl phthalate, and relative increases in weight were noted in brain, liver, kidneys, stomach, small intestines and full caecum in both sexes fed 5% diethyl phthalate. Administration of diethyl phthalate did not affect hematology, serum chemistry or urinary values, nor did it produce histologic alterations in the organs and tissues examined. In another experiment in the same study, Brown et al. (1978) fed matched pairs of six rats/sex diets containing 0 or 5% diethyl phthalate for 16 weeks. Body weights and food consumption were monitored. Rats fed 5% diethyl phthalate had significantly reduced body weights, but differences in food consumption were not significantly different from controls. From the study by Brown et al. (1978), the U.S. EPA (1987d) identified a NOAEL of 750 mg/kg/day and a LOAEL of 3160 mg/kg/day.

A reproduction and fertility assessment was conducted by NTP (1984) on CD-1 mice, following a new protocol described as "fertility assessment by continuous breeding." This method consists of four tasks: 1) a range-finding study to determine maximum tolerated dose; 2) a continuous breeding study consisting of exposure during 7 days pre-mating, followed by 98 days of cohabitation and 21 days of segregation; 3) a cross-over breeding study to determine the affected sex; and 4) a reproductive performance evaluation of controls and high-dose litters from Task 2. If adverse effects are detected in Task 2, Task 3 is performed; if not, then Task 4 is performed. Range-finding tests determined the test dose levels for Task 2 at 0.25, 1.25 and 2.5% diethyl phthalate. Because no adverse effects were noted by Task 2, Task 4 was performed. The reproductive performance evaluation consisted of controls and litters from high-dose (2.5%) dams. Exposure via the feed

to offspring (2.5%) was continued throughout Task 4. Endpoints monitored were body weight, mating behavior, reproductive performance, sperm assessment and selected organ weights. The number of litters was significantly decreased in both treated males and females. Prostate weights were significantly higher than in controls. Both sexes had significantly increased liver weights. In females, increased pituitary weights were noted.

Diethyl phthalate has been verified by U.S. EPA (1987e) as a group D chemical - not classifiable as to human carcinogenicity because of the lack of adequate animal data and no human data. Pertinent new data on human or animal exposure to diethyl phthalate were not located in the available literature. NTP (1989) reports that a 2-year skin painting toxicity study of diethyl phthalate is underway.

Di(2-ethylhexyl)phthalate

The current verified slope factor for di(2-ethylhexyl)phthalate is based on the carcinogenicity studies conducted by NTP (1980, 1982b), in which F344 rats (50/sex/group) were fed dietary levels of 0, 6000 or 12,000 ppm di(2-ethylhexyl)phthalate for 103 weeks. Also, B6C3F1 mice (50/sex/group) were fed 0, 3000 or 6000 ppm di(2-ethylhexyl)phthalate in the diet for the same length of time. Statistically significant ($p<0.01$) increased combined incidences of hepatocellular carcinomas and neoplastic nodules occurred among female rats at both doses and male rats at 12,000 ppm. A statistically significant ($p<0.01$) increase in the combined incidence of carcinomas and adenomas occurred in mice of both sexes at low and high doses. The incidence of hepatocellular adenomas was also increased in mice, the more sensitive species tested in this study, but this increase was not significant. The NTP (1982b) carcinogenicity study was subsequently published as Kluwe et al. (1982b).

Di(2-ethylhexyl)phthalate is verified as a B2 carcinogen (U.S. EPA, 1988b) - there is sufficient evidence of animal carcinogenicity, and no human data are available. Pertinent new data regarding the carcinogenicity of di(2-ethylhexyl)phthalate in humans could not be located in the available literature.

More recently di(2-ethylhexyl)phthalate was evaluated for developmental/reproductive toxicity in Fischer 344 rats and CD-1 mice (Tyl et al., 1988; Lamb et al., 1987). In both studies the LOAELs for reproductive/developmental effects were higher [1.0% of diet in rats and 0.05% in mice (Tyl et al., 1988) and 0.1% in mice (Lamb et al., 1987)] for these endpoints than that found by Carpenter et al. (1953) on which the verified oral RfD is based (U.S. EPA, 1986a). Tyl et al. (1988) tested both rats and mice and found a NOAEL in rats at 0.5% diet and a NOAEL in mice at 0.025%. The study by Lamb et al. (1987) employed a testing protocol called "fertility assessment by continuous breeding" to male and female mice (see Diethyl Phthalate section). The NOAEL in this study was 0.01% in the diet.

NTP (1989) reports that di(2-ethylhexyl)phthalate is presently undergoing further study.

Dimethyl Phthalate

Ambient water quality criteria for dimethyl phthalate are based on the 2-year oral toxicity study conducted by Lehman (1955) [incorrectly cited as Draize et al. (1948) in U.S. EPA (1980)]. Pertinent new data on this compound were not located in the available literature. Histopathologic analysis of a 2-year skin painting study in mice is being conducted by NTP (1989). Dimethyl phthalate is a verified Group D chemical - not classifiable as to human carcinogenicity because of no animal or human data (U.S. EPA, 1987f).

Di-n-octyl Phthalate

Insufficient data precluded derivation of ambient water quality criteria for di-n-octyl phthalate by the U.S. EPA (1980). Di-n-octyl phthalate is under review by the U.S. EPA RfD Work Group.

The abstract of a study conducted by Piekacz (1971), not addressed in U.S. EPA (1980), reported that 40 male and female Wistar rats were fed 0 or 3500 ppm (175 mg/kg/day) di-n-octyl phthalate in the diet for 7-12 months. An increase in kidney and liver weights was observed in females. Males and females also had an increase in serum glutamic oxaloacetic and glutamic pyruvic transaminase activities at 12 months. Histopathologic examination was apparently not performed.

No assessment of human risk from exposure to this compound has been published by the U.S. EPA. A study by DeAngelo et al. (1986) reported enhanced development of putative preneoplastic lesions in livers of rats exposed to 1% di-n-octyl phthalate. Di-n-octyl phthalate is a straight-chain isomer of di(2-ethylhexyl)phthalate, which is a verified Group B2 compound (U.S. EPA, 1988b), but, unlike di(2-ethylhexyl)phthalate, it causes little or no induction of liver peroxisomes (Mann et al., 1985; Gray et al., 1983). Strong inducers of peroxisomes have been shown to correlate with carcinogenic activity (Reddy and Lalwani, 1983; Ganning et al., 1984; Warren et al., 1982).

Gulati et al. (1985) conducted a reproductive and fertility assessment on CD-1 mice following a test protocol called "fertility assessment by continuous breeding" (see Diethyl Phthalate section). In this study, no adverse effects on reproduction, fertility or organ weights were observed in two generations of mice fed 1.25, 2.5 or 5% di-n-octyl phthalate in the diet.

Ethylphthalyl Ethylglycolate

Ambient water quality criteria were not derived for this compound by U.S. EPA (1980) because of the lack of adequate data for quantification of a BCF.

Pertinent new data regarding systemic toxicity or carcinogenicity were not located in the available literature. This chemical has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential (U.S. EPA, 1988c).

Bioconcentration Factor (BCF)

Pertinent new data concerning the BCF for butyl benzyl phthalate, dibutyl phthalate, diethyl phthtalate, di(2-ethylhexyl)phthalate and dimethyl phthalate could not be found in the available literature. Therefore, BCFs of 414, 89, 73, 130 and 36, respectively, from U.S. EPA (1980) will be used. Insufficient data precluded derivation of a BCF for di-n-octyl phthalate in U.S. EPA (1980); pertinent new data are still not available.

Log P values were estimated at 4.264 for butylphthalyl butylglycolate and 2.148 for ethylphthalyl ethylglycolate using the CLOGP program (U.S. EPA, 1987g). The equation, log BCF = (0.85 log P) - 70 (Veith et al., 1979), can be used to estimate the BCF for aquatic organisms that contain ~7.6% lipids (Veith, 1980) from log P. Using this method, steady-state BCF values are estimated to be 840 for butylphthalyl butylglycolate and 13.4 for ethylphthalyl ethylglycolate. A factor of 3.0/7.6 was used to adjust the estimated BCF from the 7.6% lipids on which the equation is based to the 3% lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCFs for butylphthalyl butylglycolate and ethylphthalyl

ethylglycolate and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans are calculated to be 332 and 5.3, respectively.

QUANTIFICATION OF EFFECTS

Butyl Benzyl Phthalate

Ambient water quality criteria were not derived for butyl benzyl phthalate by U.S. EPA (1980) because of inadequate data. New data, however, are now available from a study conducted by NTP (1985). Criteria may be derived for butyl benzyl phthalate using the verified oral RfD of 0.2 mg/kg/day (U.S. EPA, 1989) from the NTP (1985) 26-week male F344 rat study. A NOAEL for increased liver weight was identified. The NOAEL of 159 mg/kg/day divided by an uncertainty factor of 1000 (10 for subchronic to chronic extrapolation, 10 for interspecies variation and 10 to protect sensitive human subpopulations) yields the RfD value of 0.2 mg/kg/day. Using the unrounded value of 0.159 mg/kg/day for the verified oral RfD, assuming a 70 kg human consumes 2 ℓ of water and 6.5 g of fish and shellfish daily and a BCF of 414, an ambient water quality criterion of 2.37 mg/ℓ for butyl benzyl phthalate is derived. For exposure to fish and shellfish only, the criterion is 4.14 mg/ℓ.

Although pertinent new data are available (NTP, 1982a, 1985), U.S. EPA (1987b) concluded that further testing should be performed before a cancer potency factor is derived, yet recommended that a weight-of-evidence classification of C was appropriate. Group C connotates that butyl benzyl phthalate is a possible human carcinogen.

Butylphthalyl Butylglycolate

Ambient water quality criteria were not derived for butylphthalyl butylglycolate by U.S. EPA (1980) because the lack of adequate data precluded derivation of a BCF. An ADI of 700 mg/day (10 mg/kg/day) was derived from the NOEL of 1000 mg/kg/day (20,000 ppm in the diet) for rats in long-term feeding studies by Solver et al. (1950) and Hazleton Laboratories (1950) (U.S. EPA, 1980).

U.S. EPA (1986b) identified a study by the B.F. Goodrich Company (1950) as a source for deriving an oral RfD for butylphthalyl butylglycolate. This study appears to be the same as the studies used as the basis for the ADI in the AWQCD (U.S. EPA, 1980).

In this study (B.F. Goodrich Company, 1950), Sherman rats (20/group; sex not specified) were fed 0 (40 rats), 200, 2000 or 20,000 ppm butylphthalyl butylglycolate in the diet for 2 years. Because a temporary depression in growth was observed during treatment weeks 5-15, a second experiment was started in which rats were fed diets containing 0, 20, 200 or 2000 ppm butylphthalyl butylglycolate for 1 year. No treatment-related effects were observed with regard to behavior, body weight, mortality, tumor incidence, hematology and gross pathology. In the same study (B.F. Goodrich, 1950), two mongrel dogs receiving 140 mg butylphthalyl butylglycolate in capsule/day showed no adverse response. From the rat chronic study, U.S. EPA (1986b) identified a NOEL of 20,000 ppm butylphthalyl butylglycolate in the diet (1000 mg/kg/day). Applying an uncertainty factor of 1000 (10 for interspecies variation, 10 for protection of sensitive human subpopulations and 10 for the uncertainty of whether the chosen levels might be a LOAEL, because histopathologic evaluations were not performed), U.S. EPA (1986b) derived an oral RfD of 1.0 mg/kg/day. This value has been verified and is on IRIS (U.S. EPA, 1986b). It differs from the ADI derived in the AWQCD (U.S. EPA, 1980) by a factor of 10 because a larger uncertainty factor was used in deriving the verified number.

Ambient water quality criteria may be derived based on the verified RfD of 1.0 mg/kg/day and assuming exposure to 2 ℓ water/day for a 70 kg human, consumption of 6.5 g fish and shellfish daily with a BCF of 332 (see Bioconcentration Factor section), yielding a criterion of 16.8 mg/ℓ. For exposure to fish and shellfish only, the criterion is 32.4 mg/ℓ.

Dibutyl Phthalate

Ambient water quality criteria for dibutyl phthalate derived by U.S. EPA (1980) were based on data from a subchronic oral study in rats conducted by Smith (1953). Groups of 10 male Sprague-Dawley rats were fed diets containing 0, 0.01, 0.05, 0.25 and 1.25% dibutyl phthalate for 12 months. Body weights, hematology and gross and microscopic pathology were monitored. One-half of all rats exposed to 1.25% dibutyl phthalate (LOAEL) died during the first week of treatment. No other adverse effects were reported. A NOAEL of 0.25% (125 mg/kg/day) was identified, and an uncertainty factor of 100 was applied in deriving the criteria. Assuming that a 70 kg human consumes 2 ℓ water and 6.5 g of fish and shellfish daily, and assuming a BCF of 89 for dibutyl phthalate, the ambient water criterion of 34 mg/ℓ was derived. For consumption of fish and shellfish only, the criterion was 154 mg/ℓ.

New criteria may be derived from the verified oral RfD of 0.1 mg/kg/day (rounded from 0.125 mg/kg/day) for dibutyl phthalate (U.S. EPA, 1986c). Although the RfD is based on the same data from the Smith (1953) study as are the current criteria, a different uncertainty factor [1000 for the current verified RfD, as opposed to 100 applied in the U.S. EPA, (1980)] was applied. The difference results from varied views of study duration. In 1980, the study was considered equivalent to chronic duration, and therefore no uncertainty was associated with its use. The U.S. EPA (1986c) considered the study of less-than-chronic duration and stated that it had some inherent deficiencies (the example given was the use of only male animals); therefore, an uncertainty factor of 10 was added for these combined characteristics (U.S. EPA, 1986c).

Applying the unrounded verified oral RfD of 0.125 mg/kg/day, assuming a 70 kg human consumes 2 ℓ of water and 6.5 g fish and shellfish daily

with a BCF of 89, the criterion of 3.4 mg/ℓ is derived for dibutyl phthalate. For exposure to fish and shellfish only, the criterion is 15.1 mg/ℓ. Dibutyl phthalate is verified as Group D - not classifiable as to human carcinogenicity because of the lack of adequate data from human or animal exposures (U.S. EPA, 1987c).

Diethyl Phthalate

The U.S. EPA (1980) derived ambient water quality criteria for diethyl phthalate based on toxicity data from a 2-year study by Food Research Laboratories, Inc. (1955). In this study, groups of rats (15/sex, strain not reported) were fed dietary levels of 0.5, 2.5 or 5.0% (corresponding to 250, 1250 or 2500 mg/kg/day, assuming a daily food consumption equal to 5% body weight) diethyl phthalate for 104 weeks. Endpoints monitored were not reported. A NOAEL was identified at the 2.5% (1250 mg/kg/day) level. The LOAEL of 5.0% (2500 mg/kg/day) led to a small but significant reduction in growth rates without affecting food consumption. An uncertainty factor of 100 was applied to the NOAEL of 1250 mg/kg/day, and it was assumed that a 70 kg human consumes 2 ℓ of water and 6.5 g fish and shellfish daily with a BCF of 73. A criterion of 354 (~350) mg/ℓ was derived. For exposure to fish and shellfish only, the criterion was 1842 mg/ℓ.

New criteria may be derived for diethyl phthalate, using the verified oral RfD of 0.8 mg/kg/day (U.S. EPA, 1987d) from the Brown et al. (1978) 16-week rat study. A NOAEL of 1% diet (750 mg/kg/day) divided by an uncertainty factor of 1000 (10 for subchronic to chronic extrapolation, 10 for interspecies variation and 10 to protect sensitive human subpopulations) yields the RfD value, 0.75 mg/kg/day. Using this "unrounded" value of the verified oral RfD, assuming a 70 kg human consumes 2 ℓ of water and 6.5 g of fish and shellfish daily and a BCF of 73, an ambient water quality

criterion of 21.2 mg/ℓ for diethyl phthalate is derived. For exposure to fish and shellfish only, the criterion is 110.6 mg/ℓ. Diethyl phthalate has been verified by U.S. EPA (1987e) as a Group D chemical - not classifiable as to human carcinogenicity because of the lack of adequate animal data and no human data.

Di(2-ethylhexyl)phthalate

The U.S. EPA (1980) derived ambient water quality criteria for di(2-ethylhexyl)phthalate based on the study by Carpenter et al. (1953), in which guinea pigs (22-24/sex/group) were fed diets containing 0, 0.04% or 0.13% di(2-ethylhexyl)phthalate (0, 19 or 64 mg/kg/day, respectively) for 1 year. No effects were observed regarding mortality, body weight, kidney weight, or gross pathology and histopathology of the kidney, liver, lung, spleen or testes; however, treated females in both experimental groups (19 and 64 mg/kg/day) had a significant increase in relative liver weight. In the same study, Sherman rats (32/sex/group) received diets containing 0, 0.04, 0.13 or 0.4% (0, 20, 60 or 195 mg/kg/day, respectively) di(2-ethylhexyl)phthalate for 2 years. An F_1 group received the 0.04% diet for 1 year. No treatment-related effects were seen on either the parental or F_1 groups. F_0 and F_1 rats fed the 0.4% di(2-ethylhexyl)phthalate diet showed delayed growth and increased kidney and liver weights. The U.S. EPA (1980) identified a NOAEL of 60 mg/kg/day. Applying an uncertainty factor of 100 (10 each for inter- and intraspecies variability) to the NOAEL of 60 mg/kg/day for rats, and assuming a daily intake of 2 ℓ of water and 6.5 g of fish with a BCF of 130 by a 70 kg person, the ambient water criteria was established at 14.8 (~15) mg/ℓ (U.S. EPA, 1980). The U.S. EPA (1986a) derived and verified an oral RfD of 0.02 mg/kg/day for di(2-ethylhexyl)-phthalate from the same study (Carpenter et al. 1953) (see Existing Criteria

and Standards section); however, the LOAEL from the guinea pig data was chosen as the basis for the RfD since it appears that guinea pigs offer the more sensitive animal model.

Because di(2-ethylhexyl)phthalate was later found to induce hepatocellular carcinoma or adenoma in female F344/N rats and male and female C6B3F1 mice (NTP, 1980, 1982b), U.S. EPA (1982) derived a q_1^* and cancer-based ambient water quality criteria. From the incidence of hepatocellular adenoma or carcinoma in male mice (control, 14/50; low-dose, 25/48; high-dose, 29/50) reported in the NTP (1980, 1982b) 2-year bioassay, U.S. EPA (1982) calculated a q_1^* of 1.41×10^{-2} $(mg/kg/day)^{-1}$. This q_1^* (slope factor), rounded to 1.4×10^{-2} $(mg/kg/day)^{-1}$, has been verified by the Agency-wide CRAVE Work Group (U.S. EPA, 1988b).

Using the verified oral slope factor of 1.41×10^{-2}, assuming a 70 kg body weight, daily consumption of 2 ℓ of water and 6.5 g fish and shellfish and a BCF of 130, ambient water quality criteria for di(2-ethylhexyl)-phthalate remain as calculated by U.S. EPA (1982):

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (µg/ℓ)				
	0	10^{-7}	10^{-6}	10^{-5}	10^{-4}
2 ℓ of drinking water and consumption of 6.5 g of fish and shellfish	0	0.175	1.75	17.5	175
Consumption of fish and shellfish only	0	0.588	5.88	58.8	588

Dimethyl Phthalate

Ambient water quality criteria for dimethyl phthalate (U.S. EPA, 1980) were based on the study conducted by Lehman (1955) (incorrectly attributed to Draize et al., 1948). In this study, dimethyl phthalate was administered

to 20 female rats/group (strain not reported) at levels of 0, 2.0, 4.0 and 8.0% in the diet for 2 years. Using a food factor of 0.05, these levels are equivalent to 1000, 2000 or 4000 mg/kg/day. No effects were noted at the 1000 mg/kg/day dose level (NOEL). At the two higher levels, growth was slightly but significantly affected . Chronic nephritis was also noted in the 4000 mg/kg/day (LOAEL) group, but details were not reported. Applying an uncertainty factor of 100 (10 each for intra- and interspecies variability) to the NOEL of 1000 mg/kg/day, an oral ADI of 700 mg/day for a 70 kg human (10 mg/kg/day) was derived. Assuming a daily intake of 2 ℓ of water and 6.5 g fish and shellfish with a BCF of 36 for dimethyl phthalate by a 70 kg human, the ambient water criterion of 313 mg/ℓ was calculated. For exposure from consumption of fish and shellfish only, the criterion was 2991 mg/ℓ.

The ADI derived by the U.S. EPA (1980) and the available data are currently under review by the Agency-wide RfD Work Group. Until this review is completed and an RfD for oral exposure is verified, the ambient water quality criteria derived in the original AWQCD (U.S. EPA, 1980) should be retained. Dimethyl phthalate is a verified Group D chemical - not classifiable as to human carcinogenicity because of no animal or human data (U.S. EPA, 1987f).

Di-n-octyl Phthalate

Ambient water criteria for di-n-octyl phthalate cannot be derived because of the lack of data. From the only chronic study on di-n-octyl phthalate (Piekacz, 1971) (see Review of New Data section), U.S. EPA (1987b) defined a LOAEL of 175 mg/kg/day (only dose used) for liver effects in female rats. Because no details of methods or results were reported, U.S. EPA (1987b) concluded that data were insufficient for RfD derivation.

Di-n-octyl phthalate is under review by the RfD Work Group.

Ethylphthalyl Ethylglycolate

Ambient water quality criteria were not derived for ethylphthalyl ethylglycolate by U.S. EPA (1980) because the lack of adequate data precluded derivation of a BCF. An ADI of 175 mg/day for a 70 kg human (2.5 mg/kg/day) was derived from the NOEL of 250 mg/kg/day (5000 ppm in the diet) for rats in the chronic feeding study by Hodge et al. (1953) (U.S. EPA, 1980). The Agency-wide RfD Work Group has verified this ADI, rounded to 3 mg/kg/day, as the RfD for oral exposure (U.S. EPA, 1985).

In the Hodge et al. (1953) study, albino rats (ex-Wistar strain; 25/sex/group) were administered 0, 0.05, 0.5 or 5% ethylphthalyl ethylglycolate in the diet for 2 years. Hematologic studies and urinalyses were performed on seven samples collected simultaneously over the 2-year period. Gross and histologic examination of organs and tissues was performed at the end of the study. Administration of 0.05% or 0.5% ethylphthalyl ethylglycolate did not cause any adverse effects; however, rats in the 5% dietary group had decreased growth and survival rates, and developed kidney damage characterized by granular appearence, swelling and a pale yellow color. Dilation of the renal pelvis was observed along with deposits of crystalline calcium oxalate in the renal tubules. In the same study, dogs receiving daily doses of 0.01, 0.05 or 0.25 g/kg/day of ethylphthalyl ethylglycolate for 1 year showed no treatment-related effects. The NOEL and LOAEL of 0.5 and 5% (diet) were converted to 250 mg/kg/day and 2500 mg/kg/day by applying a food factor of 0.05 to the dietary levels. Applying an uncertainty factor of 100 (10 each for intra and interspecies variability) to the NOAEL of 250 mg/kg/day, U.S. EPA (1980, 1985) derived an oral RfD of 2.5 mg/kg/day (rounded to 3 mg/kg/day). This RfD has been verified and is on IRIS (U.S. EPA, 1985).

Using the verified unrounded oral RfD of 2.5 mg/kg/day, and assuming a daily intake of 2 ℓ of water and consumption of 6.5 g fish and shellfish with a BCF of 5.3 (see Review of New Data section) by a 70 kg human, the ambient water criterion of 86 mg/ℓ is derived. For exposure to fish and shellfish only, the criterion is 5080 mg/ℓ.

EXISTING STANDARDS AND CRITERIA

The Office of Drinking Water of the U.S. EPA is preparing a Drinking Water Criteria Document for phthalic acid esters. This document will contain Health Advisories and DWELs for those phthalic acid esters for which there are adequate data bases.

Butyl Benzyl Phthalate

An oral RfD of 0.2 mg/kg/day has been derived and verified (U.S. EPA, 1989) for butyl benzyl phthalate, based on a 26-week F344 rat study (NTP, 1985).

Butylphthalyl Butylglycolate

An oral RfD of 1 mg/kg/day has been derived and verified (U.S. EPA, 1986b) for butylphthalyl butylglycolate, based on data from a 2-year general toxicity study in Sherman rats (B.F. Goodrich Company, 1950).

Dibutyl Phthalate

The U.S. EPA (1986c) has verified an oral RfD of 0.1 mg/kg/day for dibutyl phthalate, based on toxicity data from Smith (1953).

The RQ for dibutyl phthalate is 10 pounds, based on aquatic toxicity data (U.S. EPA, 1988e).

ACGIH (1987) has adopted a TWA-TLV of 5 mg/m^3 for dibutyl phthalate. The OSHA (1985) PEL is 5 mg/m^3.

Diethyl Phthalate

The U.S. EPA (1987d) has derived and verified an oral RfD of 0.8 mg/kg/day for diethyl phthalate, based on a NOAEL of 750 mg/kg/day from a 16-week rat study by Brown et al. (1978).

ACGIH (1987) has adopted a TWA-TLV of 5 mg/m^3 for diethyl phthalate.

Di(2-ethylhexyl)phthalate

An oral RfD of 0.02 mg/kg/day has been derived and verified by U.S. EPA (1986a), based on a LOAEL of 19 mg/kg/day for increased relative liver weights from the Carpenter et al. (1953) subchronic study of guinea pigs.

A verified cancer slope factor of 1.4×10^{-2} has been calculated by U.S. EPA (1988b) based on the incidence of hepatocellular adenoma or carcinoma in male mice reported in the NTP (1982b) chronic feeding bioassay.

An RQ of 100 pounds has been derived for di(2-ethylhexyl)phthalate by U.S. EPA (1988d), based on potential carcinogenicity.

Dimethyl Phthalate

Dimethyl phathalate is under review by the Agency RfD Work Group.

ACGIH (1987) has adopted a TLV-TWA of 5 mg/m^3 for dimethyl phthalate. The OSHA (1985) PEL is 5 mg/m^3.

Di-n-octyl Phthalate

Pertinent guidelines and standards for di-n-octyl phthalate were not located in the available literature.

Di-n-octyl phthalate is under review by the Agency RfD Work Group.

Ethylphthalyl Ethylglycolate

An oral RfD of 3.0 mg/kg/day for ethylphthalyl ethylglycolate has been derived (U.S. EPA, 1980) and verified by U.S. EPA (1985), based on the NOEL of 250 mg/kg/day for kidney damage and reduced lifespan from a chronic oral toxicity study by Hodge et al. (1953).

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